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A 45,X Male with Y-specific DNA Translocated onto Chromosome 15

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SUMMARY

A 20-year-old male patient with chromosomal constitution 45,X, testes and normal external genitalia was examined. Neither mosaicism nor a structurally aberrant Y chromosome was observed when routine cytogenetic analysis was performed on both lymphocytes and skin fibroblasts. Y chromosome–specific single-copy and repeated DNA sequences were detected in the patient's genome by means of 11 different recombinant-DNA probes of known regional assignment on the human Y chromosome. Data indicated that the short arm, the centromere, and part of the long-arm euchromatin of the Y chromosome have been retained and that the patient lacks deletion intervals 6 and 7 of Yq. High-resolution analysis of prometaphase chromosomes revealed additional euchromatic material on the short arm of one of the patient's chromosomes 15. After in situ hybridization with the Y chromosome–specific probe pDP105, a significant grain accumulation was observed distal to 15p11.2, suggesting a Y/15 chromosomal translocation. We conclude that some 45,X males originate from Y-chromosome/autosome translocations following a break in the proximal long arm of the Y chromosome.

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INTRODUCTION

A 45,X karyotype usually results in a female phenotype, with clinical symptoms of the Turner syndrome. Rarely, however, the 45,X chromosomal constitution is associated with maleness. Such individuals have testes and normal male external genitalia. Some of the male patients diagnosed initially as 45,X later have proved to have a structurally aberrant Y chromosome (for review, see Bühler 1985). Others have been found to be mosaic for a cell line bearing a normal or abnormal Y chromosome (de la Chapelle et al. 1986; Gänshirt-Ahlert et al., in press). We are aware of 12 nonmosaic 45,X male patients (Fraccaro et al. 1966; Lo Curto et al. 1974; Subrt and Blehova 1974; Forabosco et al. 1977; Vignetti et al. 1977; Tolksdorf et al. 1980; Turleau et al. 1980; Seidel et al. 1981; Schempp et al. 1985; Sheehy et al. 1985; de la Chapelle et al. 1986; Disteche et al. 1986). In some of these cases, excess euchromatic material on an autosome was interpreted as evidence of Y-chromosome/autosome translocation (Subrt and Blehova 1974; Vignetti et al. 1977; Turleau et al. 1980; Disteche et al. 1986). Consequently, in these individuals, male sexual differentiation may be the result of Y-chromosomal segments present in the genome. DNA-hybridization probes detecting Y chromosome–specific sequences present a reliable tool to test such a mechanism. Indeed, hybridization with such Y-DNA probes have demonstrated that many XX males carry sequences derived from the short arm of the Y chromosome (Guellaen et al. 1984; Page et al. 1985; Müller et al. 1986; Vergnaud et al. 1986). In situ hybridization with a Y chromosome–specific DNA probe has shown that the Y-chromosomal material has been translocated to the short arm of an X chromosome in each of three XX males tested (Andersson et al. 1986).

We have recently reported a 20-year-old male patient with normal external genitalia and a 45,X karyotype (Schempp et al. 1985). Neither mosaicism nor structurally aberrant Y chromosome was observed when routine cytogenetic analysis was performed on lymphocytes and skin fibroblasts. However, high-resolution analysis of prometaphase chromosomes revealed additional euchromatic material on the short arm of one of the patient's chromosomes 15 (Schempp et al. 1985). Special staining studies suggested that this excess material was of Y origin.

In this report, we use Y DNA–hybridization probes to determine the portion of the Y chromosome present in this 45,X male and to demonstrate directly that the Y-chromosome DNA has been translocated to chromosome 15. Some of these findings have been presented and published in an abstract (Gal et al. 1985*b*).

MATERIAL AND METHODS

The proband (P.C.) was born in 1966 via normal term delivery. Birth weight was 2,000 g. He started to walk unaided at 22 mo, could never run well, and always had trouble in rising from a squatting position. Mental development was good, and he now attends university.

Laboratory tests of creatine phosphokinase, lactate dehydrogenase, T3, T4,

testosterone, and luteinizing and follicle-stimulating hormones all were within the normal values. Seminal fluid showed azoospermia.

When examined at 19 years of age, his weight was 54 kg, height was 154 cm, arm span was 151 cm, and occipito-frontal head circumference was 55.5 cm. There were no malformations or minor anomalies. Beard was present, although not abundant. Body hair was normally distributed. Penis was of normal size. Testes were descended and of reduced size and increased consistency. Neurologically he was stable, with very modest bilateral weakness of the thigh quadriceps, a condition that did not cause functional impairment.

Fibroblast Cultures

Fibroblasts of the patient were provided from skin biopsies by means of standard tissue-culture techniques.

DNA Extraction and Gel-Transfer Hybridization

DNA was prepared from peripheral leukocytes or cultured skin fibroblasts by means of published methods (Kunkel et al. 1977). Restriction digestion, electrophoresis, transfer, and hybridization of DNA were performed as described elsewhere (Page and de la Chapelle 1984; Gal et al. 1985*a*; Müller et al. 1986). As specified below, each hybridization probe was used at either reduced or high stringency. Reduced stringency implies that hybridizations were carried out at 42 C and that the final wash was in 0.1 × SSC, 0.1% sodium dodecyl sulfate at 55 C. High stringency implies that hybridizations were carried out at 47 C and/or that the final wash was in 0.1 × SSC, 0.1% sodium dodecyl sulfate at 65 C.

DNA-Hybridization Probes

Probe 47a (Geldwerth et al. 1985) detects highly homologous sequences on the X and Y chromosomes (locus *DXYS5*). At high stringency, 47a detects a Y-specific *Taq*I fragment of 4.3 kbp, a marker for deletion interval 1 on the short arm of the Y chromosome (Vergnaud et al. 1986).

Probe pDP61 (D. C. Page, unpublished data) is a subclone derived from plasmid 115 (Geldwerth et al. 1985), and it detects highly homologous sequences on the X and Y chromosomes (*DXYS8*). At high stringency, pDP61 detects a Y chromosome–specific *Taq*I fragment of 2.1 or 2.6 kbp, a marker for deletion interval 2 on the short arm of the Y chromosome (Vergnaud et al. 1986).

Probe 50f2 (Guellaen et al. 1984) defines multiple Y chromosome–specific loci and an autosomal locus. At reduced stringency, 50f2 detects Y chromosome–specific *Eco*RI fragments of 10 kbp (50f2/A), 7.5 kbp (50f2/B), 6 kbp (50f2/C), 4.5 kbp (50f2/D), and 1.7 kbp (50f2/E). Fragments 50f2/A and B, 50f2/D, and 50f2/C and E are markers for, respectively, deletion intervals 3 (on the short arm), 4 (including the centromere), and 6 (on the long arm) of the Y chromosome (Vergnaud et al. 1986).

Probe pDP105 (D. C. Page, unpublished data) defines multiple Y chromosome–specific loci. At low stringency, pDP105 detects many Y chromosome–

specific *Taq*I fragments. We scored for the presence or absence of *Taq*I fragments of 2.5 kbp (pDP105/A) and of 5.2 kbp (pDP105/B). Fragment pDP105/A is a marker for deletion interval 3, whereas pDP105/B is a marker for deletion interval 6 (D. C. Page, unpublished data).

Both probes Y-156 and Y-182 (Müller et al. 1986) contain purely Y chromosome–specific genomic *Hin*dIII fragments and detect sequences repeated several times on the short arm of the Y chromosome. By means of in situ hybridization both sequences have been assigned to the middle of Yp, most probably to band Yp11.2. We scored, at reduced stringency, for the presence or absence of a single *Hin*dIII fragment of 4.4 kbp (Y-156) or 1.85 kbp (Y-182).

Probe pDP34 detects highly homologous sequences on the X and Y chromosomes (*DXYS1*) (Page et al. 1982, 1984). At high stringency, pDP34 detects a Y chromosome–specific *Taq*I fragment of 15 kbp, a marker for deletion interval 4 (Vergnaud et al. 1986). Additionally, the probe reveals polymorphic 11-kbp and 12-kbp fragments assigned to bands q13-q21 of the X chromosome.

Probe pDP35 detects highly homologous sequences on the X and Y chromosomes (*DXYS1*) (Page et al. 1982, 1984). At high stringency, pDP35 detects a nonpolymorphic Y chromosome–specific *Mbo*I fragment of 2.5 kbp, a marker for deletion interval 4. Additionally, the probe reveals an X chromosome–specific 2.0-kbp fragment.

Probe pDP97 (D. C. Page, unpublished data) is a subclone derived from cosmid Y97 (Wolfe et al. 1985). At high stringency, it detects a repeated Y chromosome–specific *Eco*RI fragment of 5.5 kbp (*DYZ3*), a marker for the centromere of the Y chromosome (and for deletion interval 4; D. C. Page, unpublished data).

Probe 12f detects sequences on autosomes and on the X chromosome as well as on the Y chromosome (Bishop et al. 1984). At high stringency, 12f detects two or three Y-specific *Taq*I fragments. We scored for the presence or absence of an 8-kb Y chromosome–specific *Taq*I fragment, a marker for deletion interval 5 on the long arm of the Y chromosome (Vergnaud et al. 1986).

Probe pHY2.1 (*DYZ2* locus) (Cooke et al. 1982) contains a Y chromosome–specific repeat from the terminal heterochromatic region of the long arm. We scored, at high stringency, for the presence or absence of a 2.1-kbp Y chromosome–specific *Hae*III fragment (pHY2.1/A), a marker for deletion interval 7 (Vergnaud et al. 1986).

^{32}P-labeled probes were prepared by means of either nick-translation (Maniatis et al. 1975) or the oligonucleotide-labeling method (Feinberg and Vogelstein 1983, 1984) to a specific activity of $\sim 1\text{–}2 \times 10^8$ cpm/μg.

In Situ Hybridization

Chromosome preparations were made from cultured fibroblasts. A detailed description of the culture conditions and the BrdU treatment has been given elsewhere (Schempp and Meer 1983). The Y chromosome–specific probe pDP105 was radiolabeled with ^{3}H-dCTP and -dATP to a specific activity of 7×10^7 cpm/μg by means of the oligonucleotide-labeling technique (Feinberg and Vogelstein 1983, 1984). Hybridization and autoradiography were performed

according to a published method (Lau et al. 1985). After autoradiography, the chromosomes were identified by means of R-banding (Perry and Wolff 1974).

XG(A) Typing

This procedure was done as reported elsewhere (Race and Sanger 1975).

RESULTS

The 20-year-old patient was referred to as a 45,X male. Karyograms of the two tissues analyzed (lymphocytes and skin fibroblasts) showed him to be 45,X with no evidence of mosaicism or Y-chromosome rearrangements in 150 cells studied in each tissue (Schempp et al. 1985).

Origin of the Patient's Single X Chromosome

To determine the parental origin of the X chromosome, we examined the segregation patterns of various X-linked markers in the family. The Xg blood-group antigen (Race and Sanger 1975), XG(A), shows X linked–dominant inheritance. The father was XG(a+), whereas the proband and his mother were XG(a−) (fig. 1). This result suggests that the X chromosome of the proband is of maternal origin. We also followed the segregation of different DNA restriction-fragment-length-polymorphism (RFLP) markers previously assigned to the X chromosome. The *Taq*I RFLP at the *DXYS1* locus (detected by probe pDP34; Page et al. 1982, 1984) is characterized by two X chromosome–specific alleles, one of 11 and the other of 12 kbp. The proband has the 11-kbp allele and his mother is homozygous for the 11-kbp allele, whereas the father's X chromosome carries the 12-kbp allele (fig. 1). This is formal proof of the maternal origin of the proband's X chromosome.

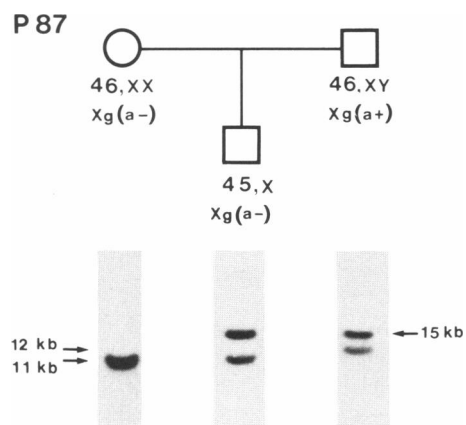

FIG. 1.—Analysis of the parental origin of the patient's single X chromosome by means of X chromosome–linked genetic markers. The segregation of the Xg blood-group antigen and the *Taq*I RFLP at the *DXYS1* locus has been followed.

DNA Studies

As seen in figure 1, a second *Taq*I restriction fragment was detected by means of the pDP34 probe in the DNA of both the patient and his father. This 15-kbp *Taq*I fragment originates from the short arm of the Y chromosome (Page et al. 1984; Vergnaud et al. 1986). This finding suggested that Y chromosome–specific DNA was present in the genome of this 45,X male, possibly translocated to another chromosome. To determine the size and the nature of this translocated Y-chromosomal segment, analysis was carried out using 11 recombinant-DNA probes of known regional assignment on the human Y chromosome.

The results of these hybridization experiments are summarized in table 1. As described in Material and Methods, many of the probes detect homologous sequences not only on the Y chromosome but also on the X chromosome and/or on autosomes. For the sake of simplicity, only the presence or absence of the Y chromosome–specific fragments has been indicated (table 1). A deletion map dividing the human Y chromosome into seven intervals has been established recently (Vergnaud et al. 1986). Intervals 1–3 and 5–7 have been assigned, respectively, to the short and long arms. Interval 4 corresponds to the centromere and the pericentromeric region. The fragments scored for in this study are grouped in table 1 according to their tentative localization in terms of this model. As shown, all seven DNA loci assigned to the short arm and examined in this study are present in the patient's DNA, as well as in his father's. Similarly, the three loci mapped to interval 4 are all present. However, of the Y-chromosomal sequences assigned to the long arm, only one of the six examined has been detected. Although the 8-kbp *Taq*I fragment detected by probe 12f, a marker for deletion interval 5, has been found, the fragments pDP105/B, 50f2/C, and 50f2/E (all of deletion interval 6), as well as that of the long-arm heterochromatic repeats (deletion interval 7), were absent.

These data indicate that this 45,X male carries deletion intervals 1–5 but lacks deletion intervals 6–7; that is, he appears to carry the entire short arm, including the male-determining region, the centromere, and the proximal long arm of the Y chromosome.

No Y-specific DNA sequences were detected in the mother, thus demonstrating that the proband inherited the Y-chromosomal material from his father. Since the patient's X chromosome is of maternal origin, the Y chromosome–specific DNA could not have been transmitted via the X chromosome of the father.

In Situ Hybridization

When, following quinacrine mustard staining, the proband's autosomes were compared to those of his parents, an additional euchromatic segment was detected on the distal short arm of one of the patient's chromosomes 15 (Schempp et al. 1985). This chromosome is designated 15p+. Cytogenetic data suggested that the extra material seen might be of Y-chromosomal origin (Schempp et al. 1985). To chromosomally map the Y-chromosomal DNA sequences present in

TABLE 1

Y-SPECIFIC DNA STUDIES

	DELETION INTERVAL													
	1	2	3		NA		4		5			6		7
DNA probes	47a	pDP61	50f2	pDP105	Y-156	Y-182	pDP34	pDP35	pDP97	50f2	12f	pDP105	50f2	pHY2.1
Restriction fragment ...			A,B	A						D		B	C,E	A
Gene locus	*DXYS5*	*DXYS8*	*DYS7*	*DYS4*			*DXYS1*	*DXYS1*	*DYZ3*					*DYZ2*
Individual:														
45,X Male	+	+	+	+	+	+	+	+	+	+	+	−	−	−
Father	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mother	NT	NT	NT	NT	−	−	−	−	NT	NT	NT	NT	NT	NT
Normal males	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Normal females	−	−	−	−	−	−	−	−	−	−	−	−	−	−

NOTE.—DNA hybridization probes were used to test these individuals for the presence (+) or absence (−) of the indicated Y-specific restriction fragments. The probes and the restriction fragments that they detect are described in Material and Methods. NA = Not yet assigned; NT = not tested.

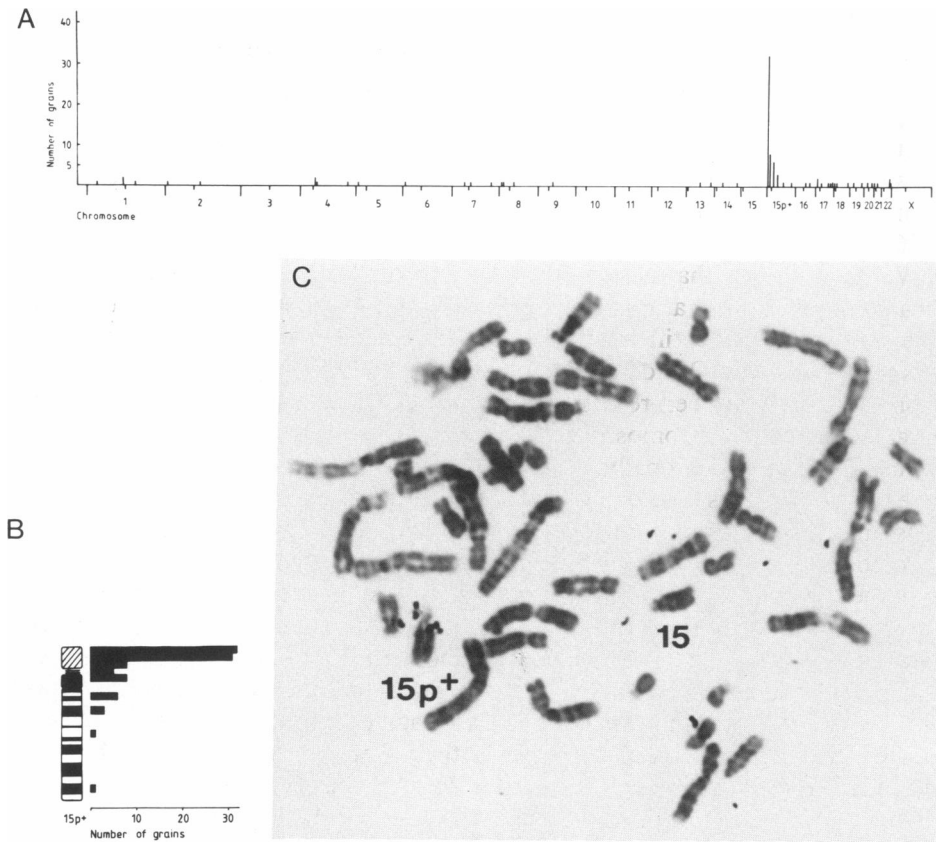

FIG. 2.—In situ hybridization with ^{3}H-labeled probe pDP105 to metaphase chromosome preparations of the proband. *A*, Histogram showing the grain distribution in 33 metaphase cells. Of 138 total grains, approximately two-thirds are located on chromosome 15p+. *B*, Diagrammatic representation of silver-grain distribution over chromosome 15p+. Three-quarters of the grains label the euchromatic material distal to 15p11.2. *C*, Karyogram of the patient. Chromosomes were identified by means of R-banding after BrdU incorporation. In this metaphase cell, the grains are distributed over the whole short arm of chromosome 15p+.

the patient's genome, in situ hybridization was performed with the ^{3}H-labeled probe pDP105. Analyses of 33 metaphase spreads revealed a significant grain accumulation on the 15p+ chromosome (fig. 2*A*). Approximately two-thirds (95 of 138) of all silver grains were found over this chromosome, which can clearly be distinguished from the normal chromosome 15 because of its characteristic early-replication-band pattern. Of the 95 grains seen over the 15p+ chromosome, three-quarters (71) were distal to band 15p11.2 (fig. 2*B*). A typical karyogram of the patient after in situ hybridization and R-banding is shown in figure 2*C*.

DISCUSSION

A male phenotype in the presence of a 45,X-chromosome constitution represents a rare and generally unexplained condition. Some of the patients diagnosed as 45,X male are, in fact, 45,X/46,XY mosaics. Low-grade or circumscribed mosaics can be overlooked by routine cytogenetic analysis. However, some such cases can be recognized by means of molecular-hybridization assays using Y chromosome–specific probes (de la Chapelle et al. 1986).

We have shown that a significant portion of the Y chromosome is translocated onto the short arm of chromosome 15 in a 45,X male. Owing to its small size, cytogenetic identification of the translocated Y-chromosomal segment was rather difficult. Our chromosome-staining findings suggested that both the short arm and the centromere had been translocated onto the nucleolus-organizer region of chromosome 15 (Schempp et al. 1985). In the present study we used a panel of regionally assigned molecular probes, each of which recognizes one or more single-copy or repeated sequences on the Y chromosome. This analysis shows that not only the short arm and the centromere of the Y chromosome but also the proximal long-arm euchromatin is present. We hypothesized previously that the breakage event resulting in this translocation might have occurred in the centromere of the Y chromosome (Schempp et al. 1985). The data presented here show that part of the long arm has also been retained. Accordingly, it seems likely that the break actually occurred in the proximal long arm. Of the two fragments resulting, one was translocated onto chromosome 15, whereas the other, consisting mostly of Yqh but lacking the centromere, was later lost. Thus, the patient's karyotype is 45,X, −15, +der(15),t(Y;15)(Ypter→Yq11.2F::15p12→15qter). The acentric segment 15pter-15p13 must also have been eliminated. No known genetic function has been yet assigned to this region (Cox and Gedde-Dahl 1985). On the other hand, it is possible that the small and atrophic testes and the azoospermia of the patient are due to the lack of deletion intervals 6 and 7 of Yq (Tiepolo and Zuffardi 1976; Fryns et al. 1985).

Most Y-chromosome/autosome translocations diagnosed by means of routine analysis involve the heterochromatic portion of the Y chromosome (Bühler 1985; Fryns et al. 1985). In most cases the Yqh is attached to an acrocentric autosome, often to the short arm of chromosome 15 or 22. These frequent associations may be the consequence of the attraction of the constitutive heterochromatin located in the long arm of the Y chromosome and in the short arm of the acrocentric chromosomes. It is worth mentioning that in another four 45,X males in whom Y-chromosome/autosome translocations were suggested, the acrocentric chromosomes 14, 15, or 22 were involved (Subrt and Blehova 1974; Koo et al. 1977; Turleau et al. 1980; Disteche et al. 1986). Furthermore, when Y chromosome–specific recombinant-DNA probes were used for filter and in situ hybridization, a 45,X male described earlier (Forabosco et al. 1977) and reexamined recently by us was seen to carry a Yp/18 translocation (Maserati et al. 1986). However, at least two cases of 45,X

males with a Y/5 chromosomal translocation (Vignetti et al. 1977; Sheehy et al. 1985) have been reported, showing that nonacrocentric chromosomes may participate in translocations of Y-chromosomal euchromatin. In addition, three 45,X males with various deletions of chromosome 5 and the clinical features of the cri du chat syndrome have been described to date (Vignetti et al. 1977; Tolksdorf et al. 1980; Seidel et al. 1981).

Recent Y-chromosomal DNA analysis of 46,XX and 45,X males has shown that most such cases are due to the translocation of a male-determining portion of the Y chromosome onto another chromosome (Guellaen et al. 1984; Page et al. 1985; Schempp et al. 1985; Andersson et al. 1986; Disteche et al. 1986; Maserati et al. 1986; Müller et al. 1986; Vergnaud et al. 1986). Although many XX males originate from an interchange between the Y and X chromosomes, many 45,X males seem to originate from Y-chromosome/autosome translocation. However, it is not necessarily the case that all XX males should necessarily derive from X/Y chromosomal interchange. Some could originate from a chromosome Y–euchromatin/autosome translocation. An X/Y chromosomal interchange in the etiology of 45,X males is unlikely, since it would require the combination of two rare events, a translocation and a nondisjunction. Additional support for this contention comes from the observation that the single X chromosome of all four 45,X males analyzed to date was of maternal origin (de la Chapelle et al. 1986; Maserati et al. 1986; present paper).

It seems likely that the site of the Y-chromosome break preceding the translocation is crucial in the etiology of 45,X males. The presence of centromere-like structures in the translocated Y-chromosomal segment has been demonstrated in at least six of the 12 45,X males reported to date (Subrt and Blehova 1974; Vignetti et al. 1977; Sheehy et al. 1985; Schempp et al. 1985; Maserati et al. 1986; Disteche et al. 1986), whereas, in a seventh case (Turleau et al. 1980), the preservation of the Y-chromosomal centromere seems probable. In all cases, the nontranslocated fragments were acentric or functionally acentric, and they have been lost during the subsequent cell divisions.

Note added in proof—Disteche et al. have recently described another 45,X male with a translocation of intervals 1–5 of the Y chromosome to 15p.

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